ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

Relationship Between Modifiable Risk Factors and Blood Cell Types in Acute Coronary Syndrome and Estimation of Mortality in Emergency Department

Akut Koroner Sendromda Değiştirilebilir Risk Faktörleri ile Kan Hücresi Tipleri Arasındaki İlişki ve Acil Serviste Mortalite Tahmini

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ABSTRACT

Aim: Inflammatory mediators such as leukocyte count (WBC), neutrophil / lymphocyte ratio (NLR), platelet / lymphocyte ratio(PLR), platelet distribution width (PDW) and C reactive protein (CRP) are used for the prediction of ischemic vascular events such as acute coronary syndrome (ACS).In this study, the relationship between inflammatory mediators and modifiable risk factors in the diagnosis of ACS and mortality was examined.

Material and methods: A total of 100 patients with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) were included in the study. Blood samples for WBC, neutrophil count, NLR, PLR, PDW and CRP and routine blood laboratory studies were taken at the time of admission of the patients.

Results: Of the patients diagnosed with ACS,49% was STEMI and 51% was NSTEMI. Female gender was found to be higher in the NSTEMI group than in the STEMI group and also the hypertension ratio was found to be higher in the NSTEMI group than in the STEMI group and it was found to be statistically significant. The NLR median value between the STEMI and NSTEMI diagnostic groups was found to be higher in the NSTEMI group and statistically more significant.

Conclusions: In conclusion; troponin, control troponin, lymphocyte and NLR ratio were found to be statistically significant between STEMI and NSTEMI diagnostic groups.In addition to this; age was found as an effective parameter on mortality.

Keywords: Acute coronary syndrome, leukocyte count, platelet distribution width

ÖZ

Amaç: Lökosit sayısı (WBC), nötrofil / lenfosit oranı (NLR), trombosit / lenfosit oranı (PLR), trombosit dağılım genişliği (PDW) ve C reaktif protein (CRP) gibi inflamatuar medyatörler; akut koroner sendrom (AKS) gibi iskemik olayların tahmininde kullanılmaktadır. Çalışmamızda , AKS tanısında inflamatuar mediatörler , çeşitli risk faktörleri ve mortalite arasındaki ilişki incelenmiştir.

Gereç ve Yöntem: Çalışmaya ST elevasyonlu miyokard enfarktüsü (STEMI) ve ST elevasyonu olmayan miyokard enfarktüsü (NSTEMI) tanısı olan toplam 100 hasta dahil edildi. Hastaların acile başvuru anındaki sırasında WBC, nötrofil sayımı, NLR, PLR, PDW,CRP değerleri ve diğer biokimyasal belirteçler için kan örnekleri alındı.

Bulgular: AKS tanısı konan hastaların% 49'u STEMI ve% 51'i NSTEMI idi. Kadın cinsiyetin NSTEMI grubunda STEMI grubuna göre daha yüksek olduğu ve hipertansiyon oranının NSTEMI grubunda STEMI grubuna göre daha yüksek olduğu ve istatistiksel olarak anlamlı olduğu saptandı. STEMI ve NSTEMI tanı grupları arasındaki NLR medyan değeri, NSTEMI grubunda daha yüksek ve istatistiksel olarak daha anlamlı bulundu.

Sonuç: Sonuç olarak; STEMI ve NSTEMI tanı grupları arasında troponin, kontrol troponin, lenfosit ve NLR oranının anlamlı farklılık gösterdiği bulunurken yaşın mortalite üzerinde etkili bir parametre olduğu görülmektedir.

Anahtar Kelimeler: Akut koroner sendrom, löosit sayısı, trombosit dağılım aralığı

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Introduction

While the underlying cause of atherosclerotic heart disease (ASHD) is thought to be endothelial damage dependent cellular proliferation, recent studies have also shown that inflammatory mechanisms play an important role in the pathogenesis of ASHD (1,2). After these developments, inflammatory mechanisms in many cardiac and non-cardiac diseases have begun to be investigated. It has been shown that inflammatory mechanisms are important in the development and prognosis of acute coronary syndrome (ACS) (1,2). It has been shown that inflammatory mediators are associated with ASHD, thrombus formation is induced, and plaque rupture risk increased. For this purpose, many inflammatory mediators such as Leukocyte and C Reactive Protein (CRP) are used in asymptomatic patients to foresee ischemic vascular events (3).

An ACS is a life-threatening table that develops after vessel erosion in the coronary arteries or after a plaque rupture and requires immediate intervention. ACS is divided into three different clinical classes: ST segment elevation MI (STEMI), usually occurring in full occlusion of coronary arteries and seen on at least two consecutive derivations of the electrocardiogram (ECG), non-ST segment elevation MI (NSTEMI) and unstable angina pectoris without enzyme elevation (USAP) (4). Chest pain is one of the frequent referrals to emergency services. However, it is not always possible to diagnose ACS in these patients. For this reason, the diagnosis and differential diagnosis of these patients is gaining importance. The ECG should be the first assessment of these patients. STEMI is often diagnosed based upon the patient's clinic and ECG findings. However, in diagnosis of NSTEMI and USAP, it is very important to use ECG findings and clinical evaluation, ECG and especially cardiac specific troponin in combination (5). In order for the level of troponin to be measurable, i.e being able to be positive, the myocardium must be damaged in significant quantities, which causes the increase in circulation level to be delayed. Because the level of troponin is measurable after 3-6 hours, 6-12 hours of sampling may be required to exclude ACS in patients with suspected ACS and those with NSTEMI (5,6). Therefore, research for new biomarkers in the diagnosis of ACS and mortality has become widespread in recent years.

In this study, the role of blood parameters such as leukocyte count (WBC), neutrophil count, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), platelet distribution width (PDW) and C reactive protein (CRP) in ACS diagnosis and mortality prediction were investigated in patients presented with chest pain to the emergency department (ED) with STEMI and NSTEMI diagnosis. The role of modifiable risk factors in predicting mortality after ACS was also investigated.

Material and Methods

A total of 100 patients with STEMI and NSTEMI who were referred to Bursa Uludag University Medical Faculty ED for 6 months were included in this prospective study. The study was approved by the Clinical Research Ethics Committee of a tertiary hospital with the decision number 2016-18/30. All patients were included in the study, including patients aged 18 years and older diagnosed with ACS who agreed to participate in this study, also patients with chest pain complaints and patients with ACS and those who met inclusion criteria were included.

Patients who were younger and who were not oriented-cooperated, who had diseases which may impair cognitive functions such as dementia, those who refused to participate in the work, pregnant women, those had a diagnosis of malignancy, those with kidney and liver disease, those with multiple organ trauma, those with active infection with fever of 38 degrees and above, those with known deep vein thrombosis (DVT) and thromboembolic disease and the patients with sepsis were excluded from the study.

In addition to the demographic information of the patients participating in the study, additional information such as history of chest pain or complaint and its characteristics, diabetes, hypercholesterolemia, hypertension, family history, smoking history, obesity, alcohol intake, previous ACS story were obtained, and additional diseases and additional complaints were questioned and recorded.

Patient's data such as; age, blood pressure(systolic and diasyolic), oxygen saturation as well as ; AST- AST levels, creatinine, CRP, CK, CK-MB, troponin levels (in the first admission time) , control troponin levels (6 hours later after the first admission), WBC, neutrophile, lymphocyte, thrombocyte, PDW, NLR, PLR were obtained in the first admission time and included in our study.

Statistical Analysis

Statistical analysis of the data was done in SPSS 23.0 statistical package program. Whether data showed normal distribution or not was examined by the Shapiro-Wilk test. T-test was used to compare two groups with normal distribution, and Mann-Whitney U test was used to compare the data without normal distribution. Pearson Chi-square test, Fisher's exact Chi-square test and Fisher-Freeman-Halton test were used in the analysis of the categorical data. The logistic regression method was used in examining the risk factors that affect mortality. Significance level was determined as $p<0.05$.

Results

Of the 100 patients included in the study, 18% were female and 82% were male. The mean age of the patients (± SD) was 58.83 ± 11.36 years. The mean age of the male patients (± SD) was 56.49 ± 10.18, while the mean age of the female patients was (± SD) 69.50 ± 10.58. There was a statistically

significant difference between the mean age of males and females and the mean age of male patients was lower than females (p <0.001). When the patients were examined according to the risk factors, smoking in 43%, hypertension (HT) in 52%, diabetes mellitus (DM) in 24%, myocardial infarction (MI) history in 24%, family history in 16% and dyslipidemia in 7% were detected. 49% of patients were diagnosed with STEMI, while 51% were diagnosed with NSTEMI. The mortality rate was determined as 7% according to the results obtained by the 4-week follow-up of the patients.

When the characteristics of the chest pain of the patients participating in the study were examined; 89% had classic anginal character, while 11% had non-classical anginal character of chest pain. When the periods of onset of chest pain of the patients participating in the study were compared, it was found that 85% of the patients had a chest pain in the first 24 hours and 15% of the patients applied to the hospital with a complaint of a chest pain lasting longer than 24 hours.

Vital findings and blood parameters were compared between the STEMI and NSTEMI diagnostic groups of the patients included in the study (Table-1). Accordingly, troponin, control troponin, lymphocyte and NLR ratio were found to be statistically significant between STEMI and NSTEMI diagnostic groups (p values: 0.004, 0.000, 0.006 and 0.049 respectively).

History parameters, admission and referral status, and mortality parameters after four weeks were compared between the diagnosis groups (Table-2). While 25.5% of the NSTEMI group were females, the rate of females in the STEMI group was lower by 10.2%. Between the diagnostic groups, there was a significant difference in females in terms of gender (p: 0.047). In the NSTEMI group, the percentage of those with HT was 62.7%, while in the STEMI group it was found to be 51%. There was a statistically significant difference between the diagnostic groups in terms of HT (p: 0.028).

When risk factors affecting mortality were examined with univariate analysis, those with significance level p <0.250 included in multivariate analysis. As a result, age, diagnosis groups and smoking were included in the model. When the risk factors affecting the four-week mortality were examined, only age was found to be statistically significant. One unit increase in the age increased the risk of death by 1.096-fold. No statistically significant difference was found in the analysis of other risk factors in terms of affecting mortality.

The statistical study we conducted on HT, smoking and DM risk groups as the main risk group for the patients included in the study; the patients without these three risk factors accounted for 16% of the total patients. According to this, 84% of the patients had at least one of these three basic risk factors. Basic blood parameters were compared in patient groups with and without these three basic risk factors. When HT, DM, and smoking were considered as the three major risk factors among the patient groups included in the study, it was found that 13 of the 16 patients in whom these risk factors were not found were male (13%) and 3 of them were female (3%) (Table 3).

According to this, there was no statistical significance between the blood parameters of patient groups with and without risk factors between male and female gender.

	NSTEMI	STEMI	p
	Median (Min-Max)	Median (Min-Max)	value
Age	58 (40-85)	57 (39-76)	0.141
Systolic BP	120 (90-200)	120 (60-170)	0.336
Diastolic BP	70 (50-100)	70 (30-100)	0.419
NDS	80 (60-120)	80 (46-105)	0.104
sO_2	95 (90-100)	96 (83-99)	0.410
AST	22 (11-155)	25 (10-226)	0.160
ALT	20 (8-85)	21(6-57)	0.505
Creatinine	0.85 (0.65-1.56)	0.9 (0.58-1.56)	0.279
CRP	0.5 (0.1-16)	0.4 (0.1-31.3)	0.639
CK	116 (21-1224)	116 (20-2853)	0.844
CK- MB	30 (10.6-219)	30 (8-226)	0.508
Troponin	120 (3.8-33312)	29.61 (1.7-50000)	**0.004***
Control Troponin	1401(43.9-50000)	36008 (2.3-116200)	**0.000***
WBC	9.9 (3.1-18.8)	11.1 (5.7-20.9)	0.068
Neutrophile	5.73 (1.7-13.1)	6.03 (2.24-13.5)	0.759
Lymphocyte	2.86 (0.002-8.15)	3.55 (0.51-8.92)	**0.006***
Thrombocyte	238 (30-378)	235 (80-359)	0.697
PDW	18.2 (15.1-20.2)	17.7 (15.2-22.9)	0.576
NLR	2.17(0.75-7.1)	1.66(0.61-12.2)	**0.049***
PLR	82000(64.16-700000)	72000(35.4-315000)	0.083

Table-1: Comparison of vital signs and some parameters among the diagnostic groups.

Discussion

Cardiovascular diseases are one of the most preeminent cause of death in the world in our age, and it is expected to be in this way for many years. Acute MI may be the first sign of coronary artery disease or may recur in people with known diseases (7,8). Many risk factors affect mortality in ACS; age, sex, previous MI history, DM, kidney failure, smoking, HT, obesity, hyperlipidemia are the main ones. Reduction of coronary artery disease risk factors along with

		NSTEMI		STEMI		
		Number (n)	Percentage (%)	Number (n)	Percentage (%)	p value
Gender	Female	13	(%25.5)	5	(%10.2)	**0.047***
	Male	38	(%74.5)	44	(%89.8)	
Characteristics	typical	47	(%92.2)	42	(%87.5)	0.517
	atypical	4	(%7.8)	7	(%12.5)	
When to start	0-5 hours	36	(%70.6)	33	(%67.3)	0.432
	6-11 hours	7	(%13.7)	6	(%12.2)	
	12-23 hours	0	(%0.0)	3	(%6.2)	
	24 hours	8	(%15.7)	7	(%14.3)	
Hypertension	No	19	(%37.3)	29	(%59.2)	**0.028***
	Yes	32	(%62.7)	20	(%40.8)	
DM	No	36	(%70.6)	40	(%81.6)	0.196
	Yes	15	(%29.4)	9	(%18.4)	
Smoking	No	32	(%62.7)	25	(%51.0)	0.236
	Yes	19	(%37.3)	24	(%49.0)	
Obesity	No	45	(%88.2)	48	(%98.0)	0.057
	Yes	6	(%11.8)	1	(% 2.0)	
Hyperlipidemia	No	46	(%90.2)	47	(%95.9)	0.437
	Yes	5	(%9.8)	2	(%4.1)	
Family History	No	41	(%80.4)	43	(%87.8)	0.315
	Yes	10	(%19.6)	6	(%12.2)	
Result	Coronary ICU hospitalization	30	(%58.8)	46	(%93.9)	**0.000***
	Referred to the hospital	21	(%41.2)	3	(%6.1)	
Mortality After 4 Weeks	Alive	48	(%94.1)	45	(%91.8)	0.712
	Exitus	3	(%5.9)	4	(%8.2)	

Table-2: Comparison of history parameters, admission and referral status, and mortality parameters after four weeks among the diagnostic groups.

suggestions such as lifestyle changes, smoking cessation, diet and weight control and strict blood pressure follow-up is also very important in reducing mortality and morbidity (9).

The mean age of the patients in this study was (± SD) 58.83 ± 11.3, 82% was male and 12% was female. In the study in which Ozel et al investigated the socio-demographic and clinical characteristics of patients with ACS who were admitted to emergency department, the mean age of the patients (± SD) was 52.4 ± 9.4, and 72.1% was male (10). In the OPERA study of Montalescot et al. investigating the differences between STEMI and NSTEMI, the mean age (± SD) was 64.63 ± 12.24, and 76% of the patients were male (11). Similar to the literature, age and male gender were found to be the most important risk factors in our study.

When the literature is reviewed, age is the most important risk factor for CAD (12,13). The mean age of the male patients (± SD) was 56.49 ± 10.18, while the mean age of the female patients was found to be (± SD) 69.50 ± 10.58. The mean age of male patients was significantly lower than that of females ($p < 0.001$), and it is consistent with the literature. Studies have shown that ACS develops in women about 5-10 years later than males and symptoms occur later (14-16). In our study, 25.5% of the NSTEMI group was female whereas the female ratio of STEMI group was found to be as lower as 10.2%. There was a significant gender difference between the diagnostic groups in terms of female gender. The number of female patients with NSTEMI was more than the number of female patients with STEMI, and this is found to be statistically significant.

When classified the ACS diagnosed patients as STEMI and NSTEMI in our study, NSTEMI was 51% while STEMI was found to be 49%, and this rate was different from the literature. In GRACE records, NSTEM were detected in 30% of the cases and STEMI were detected in 34% of the cases (17). Studies conducted in recent years show that there is a significant increase in the rate of NSTEMI in all societies and genders. In a study conducted by Bugiardini et al, NSTEMI and USAP were observed in about two thirds of patients with ACS, and STEMI was detected in one third (18). It is a fact that evaluation of patients using cardiac-specific troponin follow-up and ACS subtype classification and using some risk

scores is effective in the increase of NSTEMI rate in recent years (19). Due to the fact that the follow-up of troponin and ACS subtype in patients suspected of having ACS has been done more strictly in the emergency department of our hospital in recent years, we think that the rate of NSTEMI patients is high in our study.

Similar to other studies, HT was the most significant risk factor in this study, with a rate of 52%. Unlike other studies, it attracts the attention that smoking (43%) is in the second place in this study (11,14,20). Patients with diabetes were found to have a similar ratio (%24) with other studies. The family history and the coronary artery disease history of the person accounted for 40% of the major risk factors. The frequency of hyperlipidemia in the study was 7% which is lower than other studies. In the Opera study, the risk factors are hyperlipidemia with 49.7%, HT with 47.1%, smoking with 36%, and DM with 15.6% (11).In the studies in which Yazici et al examined the compliance of the guidelines and mortality of NSTEMI patients' treatments, HT, DM, smoking and family history were reported as 71.4%, 35.8%, 26.4% and 24.4%, respectively (20). Among the risk factors, HT is one of the most common chronic diseases in the world, and in all studies, it is ranked as one of the firsts of risk factors (14,20). In this study, HT was found high in accordance with the literature. In the NSTEMI group, the rate of HT was 62.7%, whereas in the STEMI group this rate was found to be as low as 51% and a significant difference was detected between the diagnostic groups (p: 0.028). We think that this may be due to the fact that the patients diagnosed with STEMI first applied to the hospital in the form of MI, and that they did not know they were HT patients due to the lack of routine blood pressure follow-ups. It can be said that the rate of hyperlipidemia in our study was as low as 7%, due to the fact that the lipid profile in our emergency department could not be studied, or it was not routinely studied for every patient at hospitalization.

Leukocytes and subtypes are also known as markers of inflammation in cardiovascular diseases (21). NLR is more valuable than neutrophil and lymphocyte values alone, and has been shown to be a long-term mortality marker, especially in patients with STEMI (22-24). Leukocytosis is usually associated with necrosis size, glucocorticoid level, and inflammation in coronary arteries as a result of STEMI/NSTEMI (22,25). Neutrophils are the first leukocytes to reach the damaged site in STEMI/NSTEMI, producing large quantities of inflammatory mediators regulating neutrophil inflammatory response (22). There are publications in which increased numbers of neutrophils are associated with infarct size, mechanical complications, and mortality (26,27). In this study, the median value in the NSTEMI group was found to be higher than the median value in the STEMI group in terms of change in NLR between the STEMI and NSTEMI diagnostic groups, and it was statistically significant. In general, there are many studies that high level of NLR is widespread in STEMI and NSTEMI cases. However, the number of studies examining the mean value of the NLR variable between the STEMI and NSTEMI diagnostic groups is rather limited. In a study conducted by Azab et al. (28), NLR had significant predictive value in short and long term in patients with NSTEMI. As is known, neutrophils have a short life span of about 7 hours in the circulation. Contrary to expectations, Azab et al found that there was a significant relationship between mortality and all NLR values measured at different times in the study.

The mortality rate after 4 weeks of follow-up of 100 patients evaluated in the study was found to be 7%, and it is in accordance with the literature. When the risk factors affecting the 4-week mortality in the study were analyzed univariately, only age was found statistically significant when the affecting risk factors were examined. One unit increase in the age increased the risk of death by 1.096 fold. This shows that age is one of the most important risk factors as well as an effective parameter on mortality. There was no statistically significant difference in terms of affecting mortality in the analysis of other risk factors and biochemical parameters in our study.

Conclusion

In conclusion; troponin, control troponin, lymphocyte and NLR ratio were found to be statistically significant between STEMI and NSTEMI diagnostic groups. In addition to this; age was found as an effective parameter on mortality.

Conflict of Interest: The authors declare no any conflict of interest regarding this study.

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Authors' Contribution: Conceptualization, Data curation, Project administration, Resources, Supervision, Roles/Writing - original draft, Writing - review & editing (HEL, VAD) Formal analysis, Methodology, Validation, Visualization (VAD, OK) Funding acquisition, Investigation, Methodology, Project administration, Software (HEL, VAD, OK)

Ethical Statement: The study was approved by the Clinical Research Ethics Committee of a tertiary hospital with the decision number 2016-18/30.

All authors declared that they follow the rules of Research and Publication Ethics.

	Total patients (n:100) (mean± SD)	Non-risk factor (n:16) (mean± SD)	Risk factor (n:84) (mean± SD)	p value	Non-risk factor (n:16) (mean± SD)	Hypertension (n:52) (mean± SD)	Diabetes mellitus (n:24) (mean± SD)	Smoking (n:43) (mean± SD)	Non-risk factor Male (n:13) (mean± SD)	Risk factor Male (n:49) (mean± SD)	p value	Non-risk factorFemale (n:3) (mean± SD)	Risk factor female (n:15) (mean± SD)	p value
WBC*	10.67 ± 3.17	10.73 ± 2.59	10.66 ± 3.28	0.796	10.73 ± 2.59	10.32 ± 3.07	10.44 ± 2.45	11.50 ± 3.35	11.03±2.58	11.07 ± 3.30	0.899	9.43 ± 2.65	8.79 ± 2.55	0.824
Neutrophile	6.28 ± 2.46	6.38 ± 1.96	6.26 ± 2.55	0.550	6.38 ± 1.96	6.03 ± 2.13	6.23 ± 1.81	6.50 ± 2.80	6.18 ± 1.99	6.44 ± 2.59	0.919	7.24 ± 1.90	5.48 ± 2.24	0.250
Lymphocyte	3.31 ± 1.60	3.33 ± 1.42	3.31 ± 1.64	0.703	3.33 ± 1.42	3.18 ± 1.60	3.18 ± 1.67	3.77 ± 1.57	3.76 ± 1.15	3.49 ± 1.69	0.446	1.49 ± 0.97	2.46 ± 1.03	0.446
NLR*	2.38 ± 1.84	2.67 ± 2.70	2.33 ± 1.64	0.676	2.67 ± 2.70	2.32 ± 1.53	2.27±1.21	2.20 ± 1.74	1.74 ± 0.64	2.36 ± 1.76	0.689	6.67 ± 4.78	2.17 ± 0.92	0.689
Platelets (10^3)	237 ± 62	247 ± 66	235 ± 61	0.400	247 ± 66	232 ± 69	230 ± 69	2400 ± 60	254 ± 56	232 ± 62	0.182	216 ± 108	245 ± 59	0.426
PLR*	92128 ± 78955	97044 ± 65062	91192 ± 81640	0.573	97044 ± 65062	86096 ± 44688	106982 ± 134014	7777 ± 4540	722209±13558	80081 ± 47718	0.919	204666 ± 96241	142300±158265	0.919
PDW*	18.11 ± 1.34	18.36 ± 1.44	18.06 ± 1.32	0.369	18.36 ± 1.44	18.02 ± 1.16	18.63 ± 0.98	17.87 ± 1.46	18.34±1.54	17.91 ± 1.32	0.291	18.43 ± 1.15	18.76 ± 1.10	0.574

Table-3: Investigation of basic hemogram parameters according to patient groups in the presence/absence of risk factors.

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